The utility of assessing health-related quality of life to predict cognitive decline and dementia

The utility of assessing health-related quality of life to predict cognitive decline and dementia

Short running title: HRQoL: Dementia and Cognitive Decline

Aung Zaw Zaw **Phyo** [a], David A. **Gonzalez-Chica** [b, c], Nigel P. **Stocks** [b], Elsdon **Storey** [a], Robyn L. **Woods** [a], Anne M. **Murray** [d, e], Suzanne G. **Orchard** [a], Raj C. **Shah** [f], Danijela **Gasevic** [a, g], Rosanne **Freak-Poli** [a, h †], and Joanne **Ryan** [a, i †*] on behalf of the ASPREE Investigator Group[#]

[a] School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC 3004, Australia

[b] Discipline of General Practice, Adelaide Medical School, The University of Adelaide, Adelaide, SA 5005, Australia

[c] Adelaide Rural Clinical School, The University of Adelaide, Adelaide, SA 5005, Australia

[d] Berman Center for Outcomes and Clinical Research, Hennepin HealthCare Research Institute, Hennepin HealthCare Minneapolis, Minnesota, MN 55415, United States

[e] Division of Geriatrics, Department of Medicine, Hennepin HealthCare and University of Minnesota, Minneapolis, Minnesota, MN 55415, United States

[f] Department of Family Medicine and Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, IL 60612, United States

[g] Usher Institute, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, UK

[h] Department of Epidemiology, Erasmus Medical Centre, 3015 GD, Rotterdam, The Netherlands

[i] PSNREC, Univ Montpellier, INSERM, Montpellier, 34000, France

[#]ASPREE Investigator Group listed on www.aspree.org.

[†]Contributed equally as co-senior authors

*Corresponding author: Associate Professor Joanne Ryan. Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Level 5, The Alfred Centre, 99 Commercial Road, Melbourne, Victoria, VIC 3004, Australia. Email: joanne.ryan@monash.edu

ABSTRACT

Background: Health-related quality of life (HRQoL) has been shown to predict adverse health outcome in the general population.

Objective: We examined the cross-sectional association between HRQoL and cognitive performance at baseline. Next, we explored whether baseline HRQoL predicted 5-year incident cognitive decline and dementia; and whether there were gender differences.

Methods: 19,106 community-dwelling participants from the ASPirin in Reducing Events in the Elderly (ASPREE) trial, aged 65–98 years, free of major cognitive impairments, and completed the HRQoL 12-item short-form (SF-12) at baseline (2010-2014), were followed until June 2017. The physical (PCS) and mental component scores (MCS) of SF-12 were calculated. The cognitive tests were assessed at baseline, year 1, 3, 5 and 7 or close-out visit. Cognitive decline was defined as >1.5 SD drop from baseline on any of the cognitive tests. Dementia was adjudicated according to DSM-IV criteria. Linear and Cox proportional-hazards regressions were used to examine the cross-sectional and longitudinal associations respectively.

Results: At baseline, higher PCS and MCS were associated with better cognition. Over a median 4.7-year follow-up, higher MCS was associated with a reduced risk of cognitive decline and dementia (12% and 15% respectively, per 10-unit increase) and a 10-unit higher PCS was associated with a 6% decreased risk of cognitive decline. PCS did not predict dementia incidence. Findings were not different by gender.

Conclusion: Our study found that higher HRQoL, in particular MCS, predicted a reduced risk of cognitive decline and dementia over time in community-dwelling older people.

Keywords: quality of life, health-related quality of life (HRQoL), dementia, cognitive dysfunction, cognition

INTRODUCTION

Dementia represents a major global health challenge, with nearly 10 million new dementia cases diagnosed per year worldwide [1]. The estimated number of people living with dementia globally is expected to increase in size from 50 million in 2015 to around 152 million by 2050 [1]. In addition, cognitive decline and dementia lead to a high direct cost of healthcare services, increased indirect costs of unpaid caregiving by family members, and loss in national productivity [2]. In 2015, the estimated global cost of dementia was 818 billion USD; it is expected to reach 2 trillion USD by 2030 [1]. Cognitive decline and dementia also increase the physical, psychological and social burden on caregivers, family and society. Early detection of older people at a higher risk of developing dementia or cognitive decline is also associated with quality of life [3] and could permit starting preventive interventions before symptom onset.

Health-related quality of life (HRQoL) is an individual's perception of their health status and includes physical, mental, emotional, and social domains [4]. It assesses the impact of health on individuals' lives and is useful in describing the life experiences of older adults [4, 5]. Self-reported HRQoL has been shown to predict incident cardiovascular diseases, future hospitalization and all-cause mortality in both patient and general populations [6-8]. Hence, HRQoL is not only important for well-being, but is also a measure increasingly suggested as an effective indicator for health outcomes including all-cause mortality, incident cancer, and cardiovascular disease in the primary health setting [7, 9, 10]. However, the relationship between HRQoL and cognitive function is complex. Cognitive training interventions have been found to be protective against HRQoL decline in older people [11]. On the other hand, individuals with poorer HRQoL may be less likely to engage in physical and social activities [12], and these are risk factors for cognitive decline. Poorer HRQoL may thus also be a risk factor for subsequent dementia. To our knowledge, only one prospective study has investigated the relationship between HRQoL and dementia incidence [13]. This study of 1,183 older United

States (US) adults followed over an average 4.6 years, reported that higher mental HRQoL decreased the incidence of all-cause dementia by 21% [13].

No subsequent studies have attempted to replicate these findings, nor determine whether HRQoL is associated with cognitive decline in the absence of dementia. Further research is also required to determine whether these associations differ by gender, given that women are at a higher risk of dementia [14] and may have lower HRQoL [15]. This study aims to investigate whether the physical (PCS) and mental component scores (MCS) of HRQoL are associated with baseline cognitive function; predict the 5-year risk incidence of cognitive decline and dementia; and whether there are gender differences.

MATERIALS AND METHODS

Study population

This prospective cohort study used data obtained from a five-year double-blind, randomized controlled trial of low dose aspirin as primary prevention in relatively healthy, independent community-based older participants from Australia and the US [16]. Between March 2010 and December 2014, the ASPirin in Reducing Events in the Elderly (ASPREE) trial recruited a total of 19,114 individuals aged 65 years and older (US minorities only), or 70 years and older (all others) who were free of major life-limiting diseases likely to be fatal within the next five years (e.g. cardiovascular disease, cancer) [16]. Participants also were free of a dementia diagnosis and had a Modified Mini-Mental State Examination (3MS) score of ≥78 [16]. In Australia, the sample was mainly recruited through partnerships with general practitioners, while recruitment in the US was through clinical trial and academic centers [17]. The cohort was followed prospectively until June 2017 when randomized study medication ceased. ASPREE was undertaken in accordance with the Declaration of Helsinki and approved by multiple Institutional Review Boards in Australia and the US. Aspirin was not shown to be associated with incident dementia or cognitive decline [18], and thus is not considered further in this analysis.

Determinants: Health-related Quality of Life

The validated Medical Outcomes Study 12-item short-form (SF-12, version 2) questionnaire [19] used to assess HRQoL, was completed by 99.96% of the entire ASPREE cohort at baseline.

Two summary measures ─ the PCS and MCS of the HRQoL ─ were generated using norm-based scoring methods with a mean of 50 and standard deviation of 10, with higher values representing a better HRQoL [20]. The MCS is calculated from a heavier weighting on the SF-

12 scales of vitality, social functioning, role-emotional and mental health; whereas the PCS has a heavier weighting on physical functioning, role-physical, bodily pain and general health [20].

Outcome measures

Assessment of cognitive function

Trained and accredited ASPREE staff administered the following cognitive function assessments at baseline, year 1, year 3, year 5, and year 7 or close-out visit: (a) the Modified Mini-Mental State Examination (3MS) [21, 22] to assess global cognition; (b) the Hopkins Verbal Learning Test–Revised version (HVLT-R) [23] for delayed recall episodic memory; (c) the single letter (F) Controlled Oral Word Association Test (COWAT) [24] to measure phonemic verbal fluency; and (d) the Symbol-Digit Modalities Test (SDMT) [25] of psychomotor speed.

Cognitive decline

Over the course of the study, cognitive decline was defined as a sustained drop of >1.5 SD on any of the individual cognitive tests at any follow-up, compared with the baseline score [18]. This definition did not include individuals with only a transient decline [18]. Additionally, it did not include individuals with a dementia diagnosis (as described below), and can therefore be considered a milder form of cognitive impairment than dementia – akin to the concept of Cognitive Decline No Dementia [26].

Incident dementia

Participants with a suspected dementia diagnosis (dementia trigger) over the follow-up period of the trial were defined as individuals with a 3MS score < 78 [27] or a drop of >10.15 points on the 3MS compared to their predicted score based on gender, age and education, or a report of memory concerns or other cognitive problems, or a medical diagnosis of dementia or prescription of acetylcholinesterase inhibitors. These individuals then underwent further

standardized cognitive and functional assessment as described previously [18]. Other documents gathered, when available, included laboratory test results, brain computed tomography (CT) scan or Magnetic Resonance Imaging (MRI) reports, detailed medical records and specialist notes.

The dementia adjudication committee, a panel of neurologists, neuropsychologists and geriatricians from Australia and the US, reviewed all available information and adjudicated the dementia diagnosis based on the Diagnostic and Statistical Manual for Mental Disorders, American Psychiatric Association (DSM-IV) criteria [28]. For confirmed dementia cases, the date of a suspected dementia diagnosis was used as the date of dementia incidence.

Covariates

Sociodemographic factors considered in the multivariate models included age, gender, years of education, living situation and ethno-racial group. Health-related behaviors and clinical measures which were considered: smoking status; alcohol consumption; a proxy of physical ability – average longest amount of time walking outside home without any rest in the last two weeks; hypertension; diabetes; body mass index (BMI); depressive symptom score [29] and cognitive performance.

Statistical analysis

PCS and MCS were standardized for analyses so that any result was interpreted as the association/effect for every 10-unit increase in PCS or MCS.

Linear regression models were used to examine the cross-sectional association at baseline between PCS/MCS and cognitive function. The multivariable models were adjusted for age, gender, years of education, living situation, ethno-racial group, smoking status, alcohol consumption, average longest amount of time walking outside home without any rest, hypertension, diabetes, BMI, and depressive symptoms.

Cox proportional-hazards regression models were used to examine the longitudinal associations between PCS/MCS and incident dementia, and cognitive decline. Firstly, the multivariate Cox models were adjusted for age, gender, years of education, living situation, ethno-racial group, smoking status, alcohol consumption, average longest amount of time walking outside home without any rest, hypertension, diabetes, BMI, and depressive symptom scores. Secondly, we additionally adjusted for baseline cognitive function assessed by HVLT-R delayed recall, COWAT and SDMT, aiming to control for baseline cognitive status which helps minimize reverse causation (whereby low cognitive function could lead to poorer HRQoL, and lower baseline cognition is a risk for cognitive decline).

The possible interaction between PCS/MCS and gender was fitted by including multiplicative terms between these variables in the Cox regression models. PCS and MCS were also treated in quartiles to plot the crude cumulative incidence hazard function curves. Statistical software STATA version 15.0 was used (StataCorpLP, College Station, Texas, the US).

RESULTS

Of the 19,106 included participants, over half were female (56.4%) and the majority had 12 or more years of education (54.8%) (Table 1). The mean and standard deviation of HRQoL and cognitive performance scores were 55.7 (7.1) for MCS, 48.3 (8.8) for PCS, 7.7 (2.8) for HVLT-R, 93.4 (4.6) for 3MS, 12.1 (4.6) for COWAT, and 36.7 (10.1) for SDMT respectively (Table 1).

Cross-sectional associations

Cognitive scores on the 3MS, HVLT-R and SDMT were positively associated with MCS (all p-values < 0.001), while SDMT and COWAT were associated with PCS (all p-values < 0.001) (Table 2).

Longitudinal associations

Over the 4.7-year median follow-up, there were 574 individuals with incident dementia (6.8 events per 1,000-persons-year), and 2,412 had cognitive decline (39.1 events per 1,000-persons-year). In multivariate models, a 10-unit higher MCS was associated with a 15% decrease in incident dementia risk and a 12% decrease in the risk of cognitive decline (Table 3, Figure 1 and Supplementary Figure S1). A 10-unit higher PCS was associated with a 6% decrease in the risk of cognitive decline after adjustment, including for baseline cognitive function (Table 3). The cumulative incidence hazard function curves showed consistent results (Supplementary Figure S2). PCS did not predict dementia incidence (Table 3 and Supplementary Figure S3), and findings were not different by gender (Supplementary Table S1).

DISCUSSION

In this large community sample of relatively healthy older people initially free of dementia, a higher HRQoL (both PCS and MCS) predicted a lower risk of cognitive decline, and a higher MCS, but not PCS predicted a lower risk of dementia over the 4.7-year median follow-up period.

Our observation that HRQoL (both PCS and MCS) predicted cognitive decline over time, is consistent with a prior report that a one-unit higher in overall HRQoL derived from EQ-5D was associated with a 47% decrease in the risk of general cognitive decline among 74 community-dwelling frail older Japanese people with the mean age of 81.6 (8.2) years followed for two years [30]. The concordance in findings across two very different samples indicates that the association between HRQoL and cognitive decline may be widely generalizable. In addition, given our study is the first and largest study investigating this predictive capacity of HRQoL on cognitive decline among older people from the community setting, our results bring novel findings to the field.

Our study additionally provides some of the first evidence that MCS can predict future risk of dementia. Recently, it was reported for the first time that a 10-unit higher in MCS assessed with the SF-36 was associated with a 26% decrease in the risk of incident dementia over an average 4.6-year follow-up among 1,183 older Americans [13]. Comparatively, our study found that a 10-unit higher in MCS SF-12 was associated with a 15% decrease in the incident dementia risk over 4.7-year median follow-up. The lower strength of longitudinal association observed in our study may be explained by our inclusion criteria based on which the recruited study sample consisted of apparently healthy older adults resulting in a much healthier sample. This would have not only lead to a lower incidence of dementia overall, but a sample with less chronic disease. It may be expected that the predictive power of HRQoL on dementia is higher

in individuals with more comorbidity. Nonetheless, the findings of our study align with the only other previous one [13], in demonstrating that that MCS, but not PCS was associated with the risk of dementia.

Indeed, HRQoL is used to assess an individual's perception (self-rated assessment) of their general health, and limitations in everyday activity due to physical and mental ill-health in the previous 4 weeks [20]. The MCS calculation consists of a heavier weighting on mental health-related domains of SF-12 HRQoL such as limitations in usual activities due to emotional problems and mental health [20]. MCS and PCS thus assess distinct aspects of an individual's self-rated health and well-being, which could account for the differing associations with dementia. While distinct from mental health, the MCS has been shown to be a valid screening tool for both depression and anxiety disorders in the general population [31]. Thus, as we expected, our finding of evidence in MCS predicted dementia risk reflects a wealth of literature demonstrating that midlife or late life depressive symptoms are associated with approximately two folds increase in the risk of developing dementia in older people [32, 33].

The potential pathophysiological mechanisms linking poorer MCS with dementia could involve a range of overlapping pathophysiological substrates such as vascular disease, neuroinflammatory changes, deficits of nerve growth factors high cortisol levels and amyloid accumulation [34]. In brief, neurotransmitter imbalance and hypothalamic-pituitary-adrenal axis dysregulation in depression and mental illness may cause increased amyloid precursor protein expression, decreased brain-derived neurotrophic factor expression, hippocampal cell injury and death, synaptogenesis, neurogenesis, and synaptic plasticity etc. [34, 35]. This in turn would lead to amyloid deposition, tau hyperphosphorylation and aggregation, and neurodegeneration which are the pathological hallmark of dementia [34, 35]. In addition, sleep problems are a common symptom in depression [36], and may be associated with worse MCS.

Poor sleep (quality and quantity) has been shown to be associated with amyloid deposition [37]. This might be another mechanism helping link poor MCS to an increased risk of dementia.

Limitations

Limitations of the study include the relatively short follow-up period (i.e. a median 4.7 years follow-up) to identify new dementia cases in a relatively healthy sample, since dementia has a long asymptomatic prodromal phase [38]. However, given that our cohort was healthier than the respective aging populations, the effect sizes found in our study were perhaps even under-estimated. However, it remains possible that there were other factors which were not included in this analysis, which could have influenced the findings. For example, hearing impairment which has been recognized as a risk factor for dementia [39].

Strengths

Strengths of this study include the large community-based cohort of initially healthy individuals followed prospectively with rich phenotypic data and rigorous assessment of cognitive outcome and dementia diagnosis. Thus, ensuring quality data. Furthermore, our study obtained the cognitive decline/dementia status of all ASPREE 19,106 participants who completed HRQoL at baseline, with thus no loss to follow-up over a median follow-up of 4.7 years. Another strength of this study was adjusting for cognitive function at baseline, thus helping to minimize potential reverse causation. Indeed, we found that cognition at baseline was positively associated with better HRQoL, which aligns with findings from previous cross-sectional studies [40, 41]. For example, among 5,557 community-dwelling Chinese people aged 60 years and older, lower HRQoL derived from European Quality of Life-5 Dimensions (EQ-5D) index (which does not differentiate between PCS or MCS) was associated with cognitive dysfunction (assessed using the Abbreviated Mental Test) [40]. Similarly, a study examining the 83 patients aged 34 to 86 years with head and neck cancer reported that cognitive impairment was associated with lower quality of life derived from FACT-Head and Neck

Cancer [41]. Our study suggests for the first-time differential associations between HRQoL and the underlying domains of cognitive function that each test assesses. For example, global cognition and episodic memory are predominantly tasks of general cognitive function, verbal learning and episodic memory (respectively) [22, 23], supporting their stronger association with their mental well-being. On the other hand, SDMT assesses psychomotor speed, which involves processing and motor speed abilities [42], and could account for a stronger relationship with both PCS and MCS.

Clinical implications

Our finding supports the incorporation of the SF-12 into the routine assessment of Patient-Reported Outcome Measures (PROMs) of health systems, which could enhance existing dementia risk assessment which currently uses only age, gender, blood tests and lengthy neuropsychological assessments. Together, this could enable initiation of early preventive interventions for people at high risk of cognitive decline and dementia before clinical onset. Moreover, the SF-12 comprises 12 questions using plain language, and it takes only 2-3 minutes to complete [20]. Therefore, the nature of SF-12 reduces both respondent and administrative burden [20]. Additionally, given that the SF-12 can predict health outcomes such as all-cause mortality and cardiovascular disease in general older people [9, 10, 43], the routine use of SF-12 in the health care delivery system can provide other useful information in addition to dementia risk prediction. Hence, our novel findings provide evidence in support of the decision of the Australian Commission on Safety and Quality in Health Care to incorporate the SF-12 into the annual PROMs assessment [44].

CONCLUSION

In conclusion, this large study provides some of the first evidence that higher HRQoL predicted a lower risk of cognitive decline and dementia in relatively healthy older community-dwelling people. Our novel findings also support the conclusion of prior research in both patients and the general population. Further research is recommended to explore the potential mechanisms by which HRQoL affects cognitive impairment and dementia in later life and evaluate whether interventions aimed at improving HRQoL also provide cognitive benefits. Moreover, our study also indicates the importance of further investigating the potential of interventions which improve HRQoL and whether they are effective in reducing the risk of cognitive decline and dementia incidence in community-dwelling older people. Further research in this area will be helpful for policy making and clinical management to optimize the health of our aging population.

ACKNOWLEDGEMENTS

We would like to thank the ASPREE participants who volunteered for this study, the general practitioners and staff of the medical clinics who support the study participants, and the trial staff and management team of the ASPREE study in Australia and the United States.

The ASPREE trial was mainly supported by grants from the National Institute on Aging and the National Cancer Institute at the National Institutes of Health (grant number U01AG029824); the National Health and Medical Research Council of Australia (grant numbers 334047 and 1127060); Monash University (Australia) and the Victorian Cancer Agency (Australia). Other funding resources and collaborating organizations of the ASPREE study are listed on http://www.aspree.org. AZZP is supported by Monash International Tuition Scholarship (Medicine, Nursing, and Health Sciences) and Monash Graduate Scholarship (30072360). RFP is supported by a National Heart Foundation of Australia Postdoctoral Fellowship (101927). JR is supported by a National Health and Medical Research Council Dementia Research Leader Fellowship (APP 1135727). Funders played no role in the design of the study, in the collection, analysis, and interpretation of data and in the writing of the manuscript.

CONFLICT OF INTEREST

Aung Zaw Zaw Phyo: No conflict of interest to declare

David A. Gonzalez-Chica: No conflict of interest to declare

Nigel P Stocks: No conflict of interest to declare

Elsdon Storey: No conflict of interest to declare

Robyn L. Woods: No conflict of interest to declare

Anne M. Murray: No conflict of interest to declare

Suzanne G. Orchard: No conflict of interest to declare

Danijela Gasevic: No conflict of interest to declare

Rosanne Freak-Poli: No conflict of interest to declare

Joanne Ryan: No conflict of interest to declare

Raj C. Shah: Dr. Raj C. Shah reports grants from National Institute on Aging and from the Illinois Department of Public Health, during the conduct of the study. He reports being a site principal investigator or site co-investigator for which his institution, Rush University Medical Center, is paid for his activities on Alzheimer's disease clinical trials sponsored by Amylyx Pharmaceuticals, Inc., Eli Lilly & Co., Inc., Genentech, Inc., Lundbeck, Inc., Merck & Co, Inc., Navidea Biopharmaceuticals, Novartis Pharmaceuticals, Inc., Roche Holdings AG, and Takeda Development Center Americas, Inc. that are outside the submitted work. He is also a volunteer board member for the Alzheimer's Association - Illinois Chapter.

DISCLOSURE STATEMENT

Authors contribution

AMM, RLW, ES and RCS designed and conceptualized the ASPREE study. NPS provided major role in the health-related quality of life component of ASPREE study. RLW and SGO provided major roles in the acquisition of ASPREE data. RFP and JR conceived the current study. AZZP had full access to all the data in the study and analyzed the data. AZZP, RFP and JR interpreted the data, with input from DAGC, DG, and NPS. AZZP wrote the initial manuscript draft and undertook revisions. All authors provided critical comments and approved the final version.

Data availability statement

All individual participant data (re-identifiable) that underlie the results reported in this Manuscript, are available upon request to qualified researchers without limit of time, subject to approval of the analyses by the Principal Investigators and a standard data sharing agreement. Details regarding requests to access the data will be available through the web site

(www.ASPREE.org). The data will then be made available through a web-based data portal safe haven at Monash University, Australia.

Ethical Approval

The data of the present secondary data-analysis study was from a five-year ASPREE clinical trial (Trial Registration: International Standard Randomized Controlled Trial Number Register (ISRCTN 83772183) and clinicaltrials.gov (NCT 01038583)). The current secondary data analysis has been approved by the Monash University Human Research Ethics Committee (project ID: 21714). The ASPREE trial has been approved by multiple Institutional Review Boards in Australia and the U.S.

Informed Consent

All individual participants of ASPREE clinical trial signed informed consent on participation.

Research involving human participants

ASPREE is being conducted in accordance with the Declaration of Helsinki 1964 as revised in 2008, the NHMRC Guidelines on Human Experimentation, the federal patient privacy (HIPAA) law and ICH-GCP guidelines and the International Conference of Harmonization Guidelines for Good Clinical Practice. ASPREE also follows the Code of Federal Regulations as it relates to areas of clinical research. The overall management and conduct of the ASPREE clinical trial is the responsibility of the ASPREE Steering Committee.

Consent of publication

All authors gave their approval for submission.

REFERENCES

[1] Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M (2015) *World Alzheimer Report 2015: The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends*, Alzheimer's Disease International, London.

[2] Brown L, Hansnata E, Anh La H (2017) *Economic Cost of Dementia In Australia 2016–2056*, The National Centre for Social and Economic Modelling, the Institute for Governance and Policy Analysis, University of Canberra, Australia, Canberra.

[3] Mate KE, Pond CD, Magin PJ, Goode SM, McElduff P, Stocks NP (2012) Diagnosis and disclosure of a memory problem is associated with quality of life in community based older Australians with dementia. *Int Psychogeriatr* **24**, 1962-1971.

[4] Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, Bullinger M, Kaasa S, Leplege A, Prieto L, Sullivan M (1998) Cross-Validation of Item Selection and Scoring for the SF-12 Health Survey in Nine Countries: Results from the IQOLA Project. *J Clin Epidemiol* **51**, 1171-1178.

[5] Ebrahim S (1995) Clinical and public health perspectives and applications of health-related quality of life measurement. *Soc Sci Med* **41**, 1383-1394.

[6] Tsai YC, Hung CC, Hwang SJ, Wang SL, Hsiao SM, Lin MY, Kung LF, Hsiao PN, Chen HC (2010) Quality of life predicts risks of end-stage renal disease and mortality in patients with chronic kidney disease. *Nephrol Dial Transplant* **25**, 1621-1626.

[7] Phyo AZZ, Freak-Poli R, Craig H, Gasevic D, Stocks N, Gonzalez-Chica DA, Ryan J (2020) Quality of Life and mortality in the general population: a systematic review and meta-analysis. *BMC Public Health* **20**, 1596.

[8] Rodríguez-Artalejo F, Guallar-Castillón P, Pascual CR, Otero CM, Montes AO, García AN, Conthe P, Chiva MO, Banegas JR, Herrera MC (2005) Health-Related

Quality of Life as a Predictor of Hospital Readmission and Death Among Patients With Heart Failure. *Arch Intern Med* **165**, 1274-1279.

[9] Ul-Haq Z, Mackay DF, Pell JP (2014) Association between physical and mental health-related quality of life and adverse outcomes; a retrospective cohort study of 5,272 Scottish adults. *BMC Public Health* **14**, 1197.

[10] Pinheiro L, Reshetnyak E, Sterling M, Richman J, Kern L, Safford M (2019) Using health-related quality of life to predict cardiovascular disease events. *Qual Life Res* **28**, 1465-1475.

[11] Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Stoddard A, Tennstedt SL (2006) The ACTIVE Cognitive Training Trial and Health-Related Quality of Life: Protection That Lasts for 5 Years. *J Gerontol A Biol Sci Med Sci* **61**, 1324-1329.

[12] Anokye NK, Trueman P, Green C, Pavey TG, Taylor RS (2012) Physical activity and health related quality of life. *BMC Public Health* **12**, 624.

[13] Ezzati RA, Zammit JA, Katz AM, Derby EC, Zimmerman BM, Lipton BR (2019) Health-related Quality of Life, Cognitive Performance, and Incident Dementia in a Community-based Elderly Cohort. *Alzheimer Dis Assoc Disord* **33**, 240-245.

[14] Podcasy JL, Epperson CN (2016) Considering sex and gender in Alzheimer disease and other dementias. *Dialogues Clin Neurosci* **18**, 437-446.

[15] Cherepanov D, Palta M, Fryback DG, Robert SA (2010) Gender differences in health-related quality-of-life are partly explained by sociodemographic and socioeconomic variation between adult men and women in the US: evidence from four US nationally representative data sets. *Qual Life Res* **19**, 1115-1124.

[16] McNeil JJ, Woods RL, Nelson MR, Murray AM, Reid CM, Kirpach B, Storey E, Shah RC, Wolfe RS, Tonkin AM, Newman AB, Williamson JD, Lockery JE, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Trevaks RE,

Orchard SG, Beilin LJ, Donnan GA, Gibbs P, Johnston CI, Grimm RH (2017) Baseline Characteristics of Participants in the ASPREE (ASPirin in Reducing Events in the Elderly) Study. *J Gerontol A Biol Sci Med Sci* **72**, 1586-1593.

[17] Grimm R, McNeil JJ, Applegate W, Beilin L, Espinoza S, Johnston CI, Kirpach B, Margolis K, Murray A, Nelson MR, Reid CM, Shah R, Storey E, Tonkin AM, Wilson P, Wolfe R, Woods RL, Abhayaratna W, Ames D, Cobiac L, Donnan G, Gibbs P, Head R, Krum H, Jelnik M, Malik M, Williamson J, Eaton C, Weissfeld J, MacRae F, Rodriguez LM, Shah R, Newman A, Demons J, Workman B, Wood E, Satterfield S, Ernst M, Gilbertson D, Lockery JE, Shah RC, Ernst M, Hannah J, Newman A, Radziszewska B, Shah R, Thomas A, Gill G, Jackson C, Kidd M, Russell G, Pressman G, Figueredo V, Oberoi M, Ahmad M, Krstevska S, Lawson C, Katzman S, Powell J, Lang M, Bolin P, Atlanta VA, Le A, Johnson T, Thomas A, Kruger D, Obisesan T, Allard J, Dodd K, Ott B, Pemu P, Radziszewska B, Hadley E, Romashkan SV, Palaniappan L, Jose P, Church T, Myers V, Monce R, Britt N, Gupta A, Keller J, Shah RC, Lewis B, Shikany J, Allman R, Anton S, Pahor M, Burns J, Swerdlow R, Anderson H, Wiggins J, Nyquist L, Peterson KA, Newman AB, Tindle H, Johnson KC, Womack C, Birnbaum L, Nesbitt S, Volpi E, Applegate WB, Flack J, Ference B, Singh M, Lichtenberg P, Aloia J, Mikhail M, Anwarrulah AA, Trevaks RE, Fitzgerald SM, Stocks N (2013) Study design of ASPirin in Reducing Events in the Elderly (ASPREE): A randomized, controlled trial. *Contemp Clin Trials* **36**, 555-564.

[18] Ryan J, Storey E, Murray AM, Woods RL, Wolfe R, Reid CM, Nelson MR, Chong TTJ, Williamson JD, Ward SA, Lockery JE, Orchard SG, Trevaks R, Kirpach B, Newman AB, Ernst ME, McNeil JJ, Shah RC (2020) Randomized placebo-controlled

trial of the effects of aspirin on dementia and cognitive decline. *Neurology* **95**, e320-e331.

[19] Ware JE, Jr. , Kosinski M, Keller SD (1996) A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. *Med Care* **34**, 220-233.

[20] Ware JE, Jr., Kosinski M, Turner-Bowker DM, Gandek B (2002) *User's Manual for the SF-12v2® Health Survey With a Supplement Documenting SF-12® Health Survey)*, QualityMetric Incorporated, Lincoln, RI.

[21] Ryan J, Woods RL, Britt C, Murray AM, Shah RC, Reid CM, Kirpach B, Wolfe RS, Nelson MR, Lockery JE, Orchard SG, Trevaks RE, McNeil JJ, Storey E (2019) Normative performance of healthy older individuals on the Modified Mini-Mental State (3MS) examination according to ethno-racial group, gender, age, and education level. *Clin Neuropsychol* **33**, 779-797.

[22] Teng EL, Chui HC (1987) The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry* **48**, 314-318.

[23] Benedict RHB, Schretlen D, Groninger L, Brandt J (1998) Hopkins Verbal Learning Test - Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. *Clin Neuropsychol* **12**, 43-55.

[24] Ross TP (2003) The reliability of cluster and switch scores for the Controlled Oral Word Association Test. *Arch Clin Neuropsychol* **18**, 153-164.

[25] Smith A (1982) *Symbol Digit Modalities Test (SDMT). Manual (revised)*, Weestern Psychological Services, Los Angeles.

[26] Graham JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, McDowell I (1997) Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* **349**, 1793-1796.

[27] Bland RC, Newman SC (2001) Mild Dementia or Cognitive Impairment: The Modified Mini-Mental State Examination (3MS) as a Screen for Dementia. *Can J Psychiatry* **46**, 506-510.

[28] American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders : DSM-IV*, American Psychiatric Association, Washington, DC.

[29] Radloff LS (1977) The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas* **1**, 385-401.

[30] Kitamura K, Nakamura K, Ueno K, Nishiwaki T (2016) Cognitive function is maintained in noninstitutionalized elderly Japanese requiring care with high levels of health-related quality of life. *Environ Health Prev Med* **21**, 585-590.

[31] Gill SC, Butterworth P, Rodgers B, Mackinnon A (2007) Validity of the mental health component scale of the 12-item Short-Form Health Survey (MCS-12) as measure of common mental disorders in the general population. *Psychiatry Res* **152**, 63-71.

[32] Bennett S, Thomas AJ (2014) Depression and dementia: Cause, consequence or coincidence? *Maturitas* **79**, 184-190.

[33] Ownby. RL, Crocco. E, Acevedo. A, John. V, Loewenstein D (2006) Depression and Risk for Alzheimer Disease: Systematic Review, Meta-analysis, and Metaregression Analysis. *Arch Gen Psychiatry* **63**, 530-538.

[34] Linnemann C, Lang UE (2020) Pathways Connecting Late-Life Depression and Dementia. *Front Pharmacol* **11**, 279.

[35] Dafsari FS, Jessen F (2020) Depression-an underrecognized target for prevention of dementia in Alzheimer's disease. *Transl Psychiatry* **10**, 160-160.

[36] Nutt D, Wilson S, Paterson L (2008) Sleep disorders as core symptoms of depression. *Dialogues Clin Neurosci* **10**, 329-336.

[37] Sprecher KE, Koscik RL, Carlsson CM, Zetterberg H, Blennow K, Okonkwo OC, Sager MA, Asthana S, Johnson SC, Benca RM, Bendlin BB (2017) Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. *Neurology* **89**, 445-453.

[38] Chertkow H, Feldman HH, Jacova C, Massoud F (2013) Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: consensus from the Canadian conference on diagnosis of dementia. *Alzheimers Res Ther* **5**, S2.

[39] Thomson RS, Auduong P, Miller AT, Gurgel RK (2017) Hearing loss as a risk factor for dementia: A systematic review. *Laryngoscope Investig Otolaryngol* **2**, 69-79.

[40] Chen-Wei P, Xingzhi W, Qinghua M, Hong-Peng S, Yong X, Pei W (2015) Cognitive dysfunction and health-related quality of life among older Chinese. *Sci Rep* **17301**

[41] Williams AM, Lindholm J, Cook D, Siddiqui F, Ghanem TA, Chang SS (2017) Association Between Cognitive Function and Quality of Life in Patients With Head and Neck Cancer. *JAMA Otolaryngol Head Neck Surg* **143**, 1228-1235.

[42] Sheridan L, Fitzgerald H, Adams K, Nigg J, Martel M, Puttler L, Wong M, Zucker R (2006) Normative Symbol Digit Modalities Test performance in a community-based sample. *Arch Clin Neuropsychol* **21**, 23-28.

[43] Phyo AZZ, Ryan J, Gonzalez-Chica DA, Woods RL, Reid CM, Nelson MR, Murray AM, Gasevic D, Stocks NP, Freak-Poli R (2021) Health-Related Quality of Life and All-Cause Mortality among Older Healthy Individuals in Australia and the United States: A Prospective Cohort Study. *Qual Life Res* **https://doi.org/10.1007/s11136-020-02723-y**.

[44] Williams K, Sansoni J, Morris D, Grootemaat P, Thompson C (2016) *Patient-reported outcome measures: Literature review*, Australian Commission on Safety and Quality in Health Care (ACSQHC), Sydney.

Table 1. Baseline characteristics of participants N = 19,106

Baseline Characteristics	Participants Number (%) or Mean (SD)
Sociodemographic factors	
Age in years; median (interquartile range)	74 (71.6-77.7)
Gender	
Male	8,329 (43.6 %)
Female	10,777 (56.4 %)
Years of Education	
Under 12 years	8,634 (45.2 %)
12 years and above	10,471 (54.8 %)
Living Situation	
At home alone	6,249 (32.7 %)
With family or others	12,857 (67.3 %)
Race and Ethnicity	
White Australian	16,355 (85.6 %)
White American	1,088 (5.7 %)
Black	900 (4.7 %)
Hispanic/Latino; Asiatic; Other [a]	763 (4.0 %)
Health-related Behaviours	
Smoking Status	
Never	10,575 (55.4 %)

Baseline Characteristics	Participants Number (%) or Mean (SD)
Former	7,796 (40.8 %)
Current	735 (3.9 %)
Alcohol Consumption	
Never / Former	4,468 (23.4 %)
Current	14,638 (76.6 %)
Average longest amount of time walking outside home without any rest (last 2 weeks)	
No Walking	839 (4.4 %)
<= 15 min/day	2,341 (12.3 %)
16 – 30 min/day	4,144 (21.7 %)
> 30 min/day	11,741 (61.6 %)
Clinical Measures	
Hypertension [b]	
Yes	14,191 (74.3 %)
No	4,915 (25.7 %)
Diabetes [c]	
Yes	2,044 (10.7 %)
No	17,062 (89.3 %)
Body Mass Index (kg/m^2)	28.1 (4.7)
Centre for Epidemiologic Studies Depression Scale (CES-D-10) score	3.2 (3.3)

Baseline Characteristics	Participants Number (%) or Mean (SD)
Health-related quality of life	
Mental Component Scores (MCS)	55.7 (7.1)
Physical Component Scores (PCS)	48.3 (8.8)
Cognitive Function Tests	
Hopkins Verbal Learning Test (HVLT) Delayed Recall	7.7 (2.8)
Modified Mini-Mental State Examination (3MS)	93.4 (4.6)
Controlled Oral Word Association Test (COWAT)	12.1 (4.6)
Symbol Digit Modalities Test (SDMT)	36.7 (10.1)

[a] Other included Hispanic, Latino, Asiatic, Aboriginal and Torres Strait Islander, Native Hawaiian, other Pacific Islander, Maori, American Indian, or more than one race; [b] Hypertension = SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or on treatment for high blood pressure; [c] Diabetes mellitus = self-report of diabetes or fasting glucose ≥ 126 mg/dL or on treatment for diabetes.

Table 2. Association between cognitive function tests with mental (MCS) and physical component scores (PCS) of SF-12

	Modified Mini-Mental State Examination (3-MS)	Hopkins Verbal Learning Test (HVLT-R) delayed recall	Controlled Oral Word Association Test (COWAT)	The Symbol Digit Modalities Test (SDMT)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
MCS				
Crude	0.25 (0.16, 0.34)	0.12 (0.06, 1.18)	0.05 (-0.04, 0.14)	0.82 (0.62, 1.02)
Adjusted [a]	0.18 (0.09, 0.28)	0.13 (0.07, 0.19)	0.08 (-0.02, 0.18)	0.69 (0.48, 0.90)
PCS				
Crude	0.28 (0.21, 0.36)	0.13 (0.08, 0.18)	0.28 (0.21, 0.36)	1.64 (1.47, 1.80)
Adjusted [a]	-0.01 (-0.08, 0.07)	0.02 (-0.03, 0.07)	0.15 (0.07, 0.23)	0.90 (0.73, 1.06)

Abbreviations: MCS, mental component score; PCS, physical component score. [a] Adjusted for age, gender, education, living situation, ethno-racial group, smoking, alcohol, average longest amount of time walking outside home without any rest (last 2 weeks), hypertension, diabetes, BMI, and depressive symptom score.

Table 3. Hazard ratios for dementia, and cognitive decline by a 10-unit increase in SF-12 mental (MCS) and physical component scores (PCS)

	Dementia			Cognitive Decline [c]		
MCS	N	no. of events	Hazard Ratio (95% CI)	N	no. of events	Hazard Ratio (95% CI)
Crude	19,106	574	0.79 (0.71 – 0.88)	17,471	2,412	0.86 (0.81 – 0.90)
Adjusted [a]	18,973	571	0.80 (0.70 – 0.90)	17,355	2,390	0.89 (0.84 – 0.94)
Adjusted [b]	18,804	564	0.85 (0.76 – 0.96)	17,213	2,363	0.88 (0.83 – 0.94)
PCS						
Crude	19,106	574	0.92 (0.84 – 1.00)	17,471	2,412	0.87 (0.84 – 0.91)
Adjusted [a]	18,973	571	1.03 (0.93 – 1.14)	17,355	2,390	0.95 (0.90 – 0.99)
Adjusted [b]	18,804	564	1.06 (0.95 – 1.17)	17,213	2,363	0.94 (0.89 – 0.99)

Abbreviations: MCS, mental component score; PCS, physical component scores. [a] Adjusted for age, gender, education, living situation, ethno-racial group, smoking, alcohol, average longest amount of time walking outside home without any rest (last 2 weeks), hypertension, diabetes, BMI, and depressive symptom score; [b] Adjusted for age, gender, education, living situation, ethno-racial group, smoking, alcohol, average longest amount of time walking outside home without any rest (last 2 weeks), hypertension, diabetes, BMI, depressive symptom score and cognitive function at baseline assessed by HVLT-R delayed recall, COWAT and SDMT; [c] Cognitive decline in individuals without dementia.

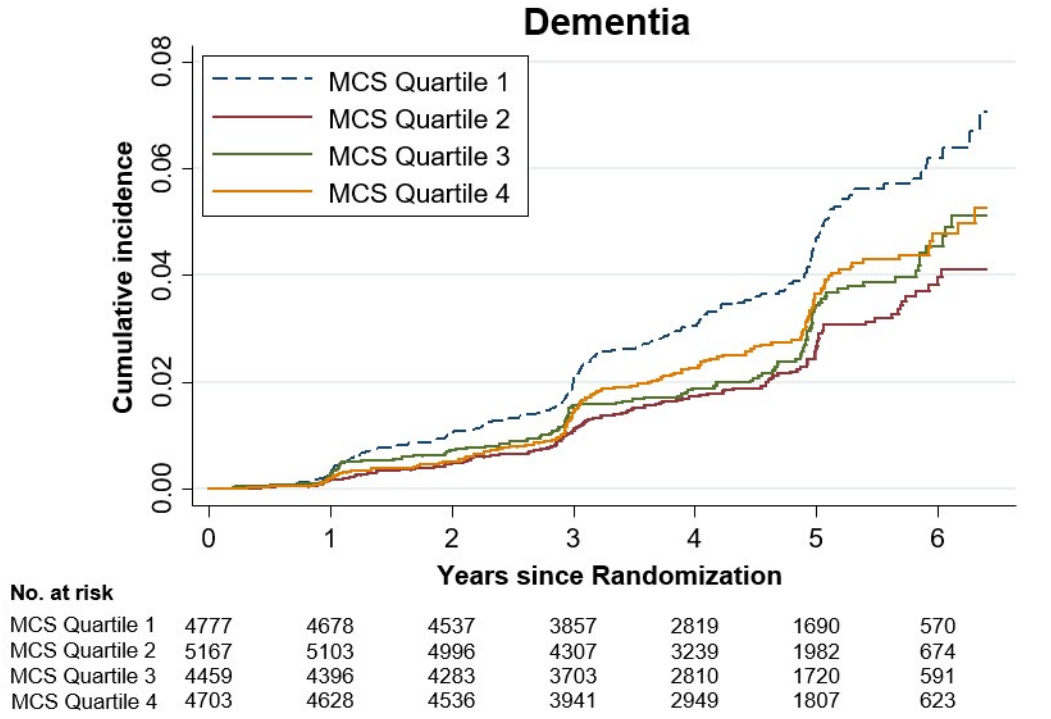


Figure 1. Crude Cumulative incidence of dementia according to the mental component score (MCS) quartiles. MCS, Mental component score. Quartile 1 = Lowest; Quartile 4 = Highest.

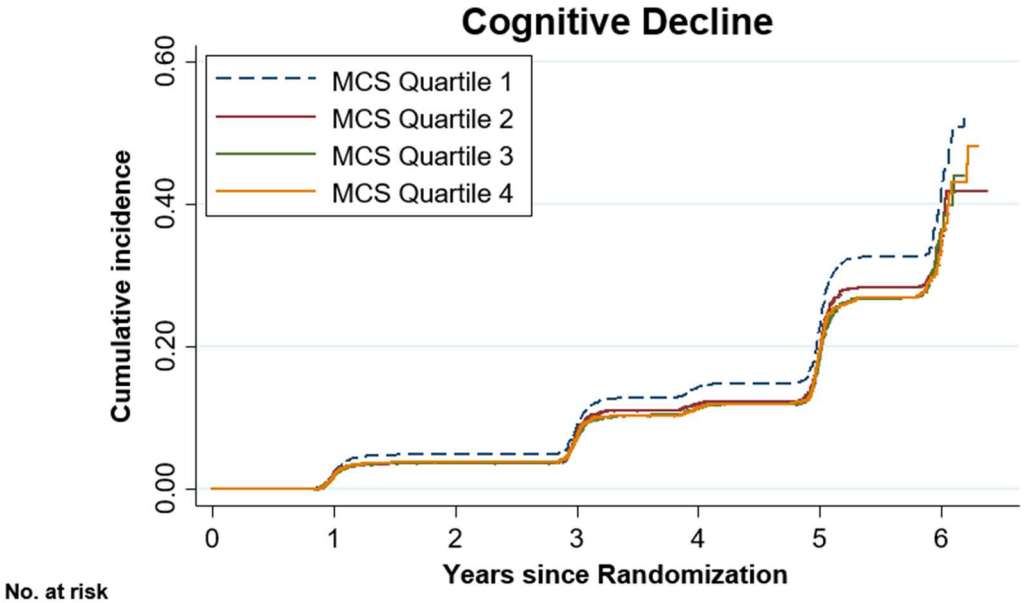
Supplementary data mentioned in the text are available in the supplementary materials.

SUPPLEMENTARY MATERIALS

Table S1. Adjusted hazard ratios for dementia, and cognitive decline by a 10-unit increase in SF-12 mental (MCS) and physical component scores (PCS) according to gender

	Male			Female			P-value [c]
	N	no. of events	Hazard Ratio [a] (95% CI)	N	no. of events	Hazard Ratio [a] (95% CI)	
Dementia							
MCS	8,203	268	0.82 (0.68 – 0.98)	10,601	296	0.89 (0.76 – 1.05)	0.92
PCS	8,203	268	1.02 (0.88 – 1.19)	10,601	296	1.09 (0.95 – 1.25)	0.62
Cognitive Decline [b]							
MCS	7,531	1,062	0.88 (0.80 – 0.97)	9,682	1,301	0.88 (0.81 – 0.95)	0.88
PCS	7,531	1,062	0.97 (0.90 – 1.05)	9,682	1,301	0.92 (0.86 – 0.98)	0.34

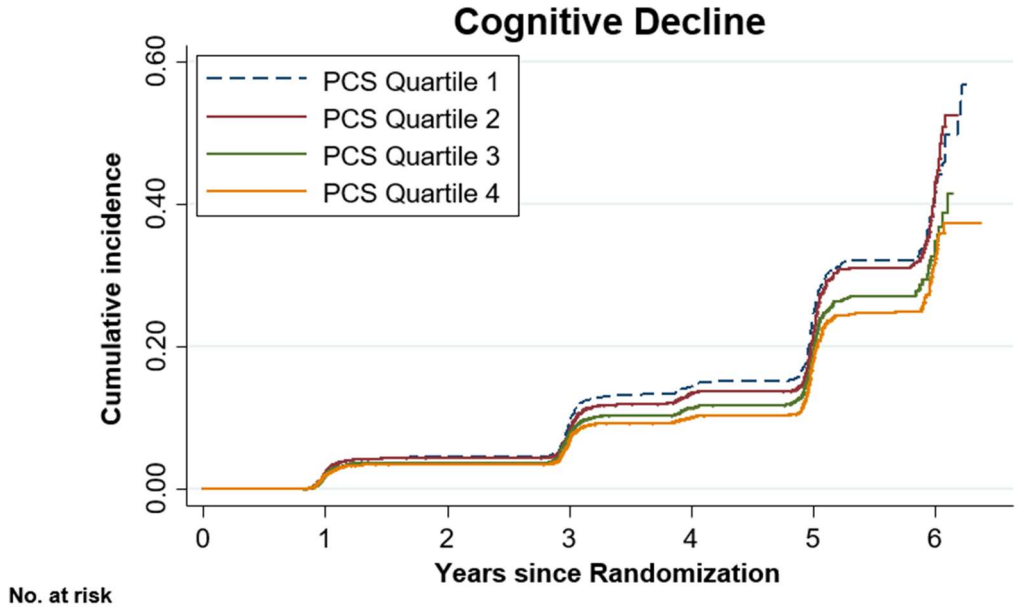
Abbreviations: MCS, mental component score; PCS, physical component score. [a] Adjusted for age, education, living situation, ethno-racial group, smoking, alcohol, average longest amount of time walking outside home without any rest (last 2 weeks), hypertension, diabetes, BMI, depressive symptom score and cognitive function at baseline assessed by HVLT-R delayed recall, COWAT and SDMT; [b] Cognitive decline in individuals without dementia; [c] P-value for gender interaction.



No. at risk

MCS Quartile 1	4261	3758	3353	2387	1556	759	96
MCS Quartile 2	4770	4248	3878	2834	1898	887	103
MCS Quartile 3	4119	3687	3370	2473	1685	782	98
MCS Quartile 4	4321	3876	3531	2580	1738	819	100

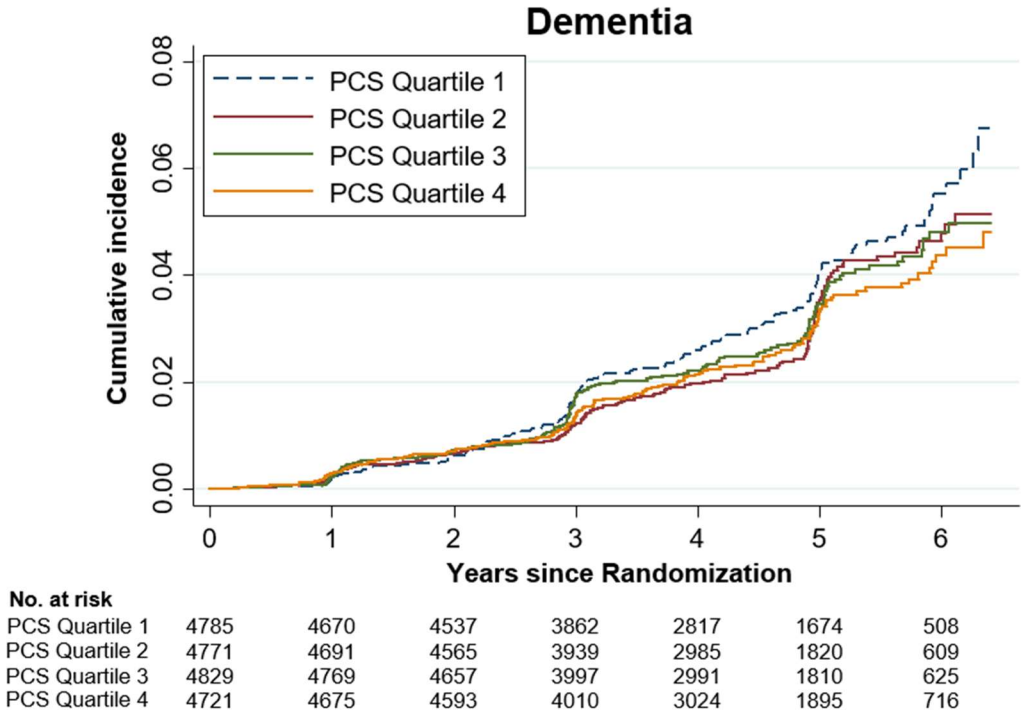
Figure S1. Crude Cumulative incidence of cognitive decline according to the mental component score (MCS) quartiles. MCS, Mental component score. Quartile 1 = Lowest, Quartile 4 = Highest.



No. at risk

PCS Quartile 1	4269	3770	3366	2406	1550	712	75
PCS Quartile 2	4350	3865	3501	2550	1733	822	91
PCS Quartile 3	4454	3974	3607	2639	1749	835	107
PCS Quartile 4	4398	3960	3658	2679	1845	878	124

Figure S2. Crude Cumulative incidence of cognitive decline according to the physical component score (PCS) quartiles. PCS, Physical component score. Quartile 1 = Lowest, Quartile 4 = Highest.



No. at risk							
PCS Quartile 1	4785	4670	4537	3862	2817	1674	508
PCS Quartile 2	4771	4691	4565	3939	2985	1820	609
PCS Quartile 3	4829	4769	4657	3997	2991	1810	625
PCS Quartile 4	4721	4675	4593	4010	3024	1895	716

Figure S3. Crude Cumulative incidence of dementia according to the physical component score (PCS) quartiles. PCS, Physical component score. Quartile 1 = Lowest, Quartile 4 = Highest.

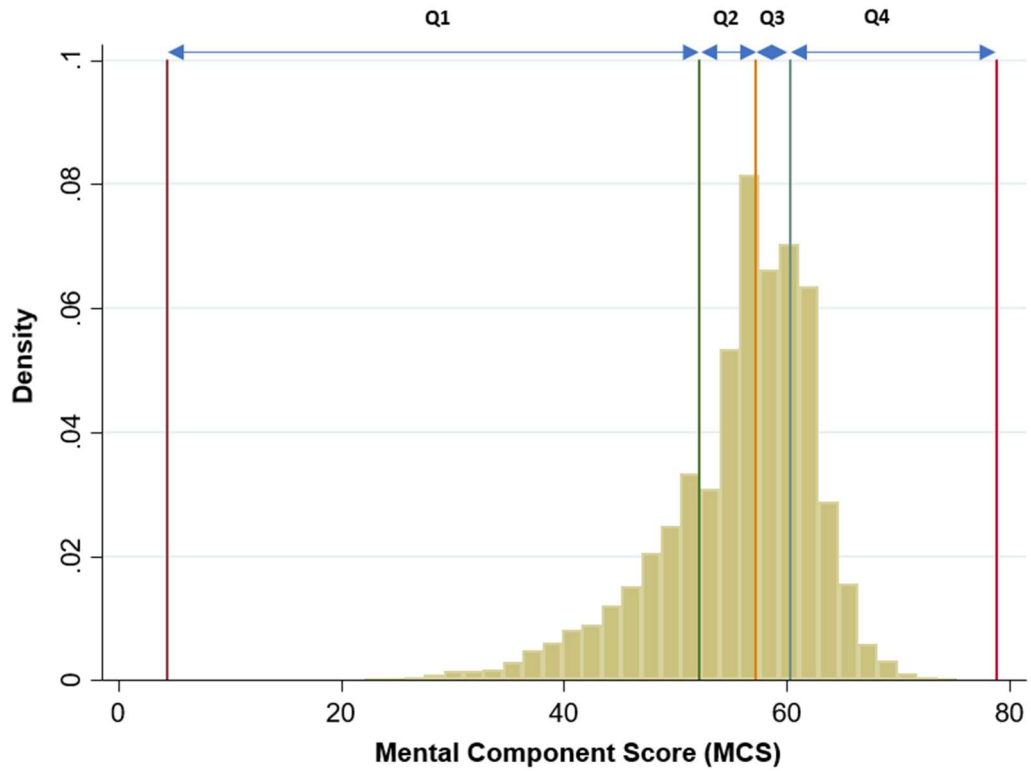


Figure S4. Histogram of mental component score (MCS) with quartiles. Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4. Quartile 1 = Lowest, Quartile 4 = Highest.

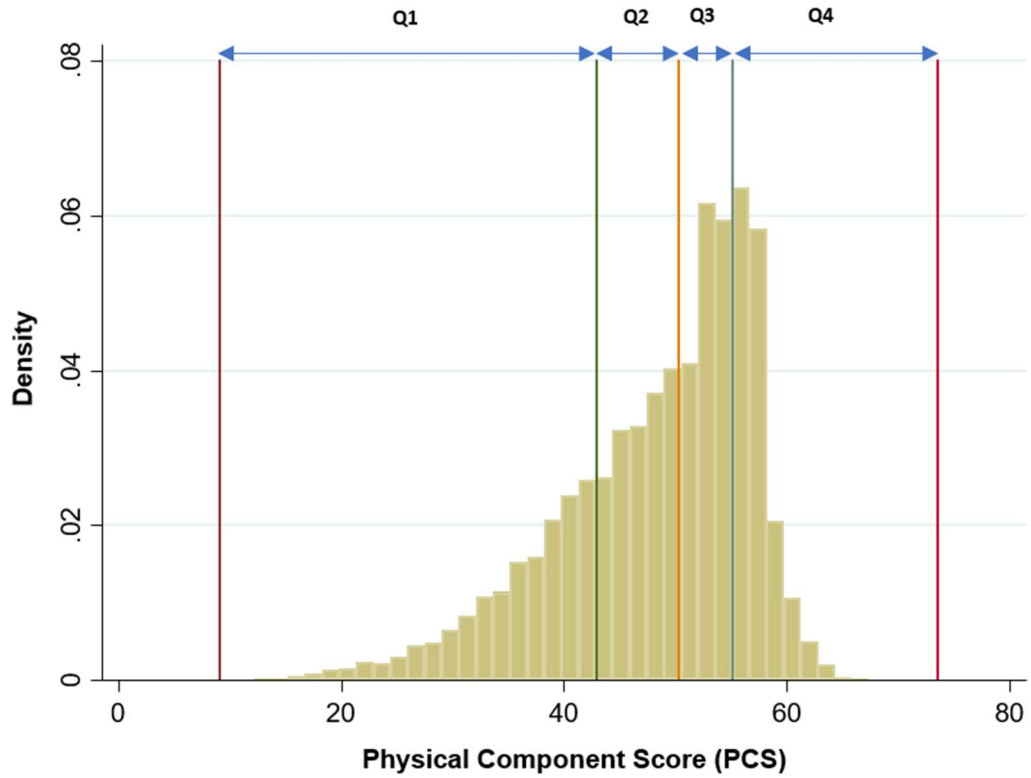


Figure S5. Histogram of physical component score (PCS) with quartiles. Q1, Quartile 1; Q2, Quartile 2; Q3, Quartile 3; Q4, Quartile 4. Quartile 1 = Lowest, Quartile 4 = Highest.